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ORIGINAL ARTICLE

Functional anatomy of outcome evaluation during Iowa Gambling Task performance in patients with Parkinson's disease: an fMRI study

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Abstract The aim of this study was to investigate the functional anatomy of decision-making during the Iowa Gambling Task in patients with Parkinson's disease. We used event-related functional magnetic resonance imaging (fMRI) during a computerized version of IGT to compare 18 PD patients on dopaminergic medication in the ON state and 18 healthy control subjects. Our analyses focused on outcome evaluation following card selection, because we expected this aspect of decision-making to be impaired in PD patients. The PD patients exhibited lower activation of the left putamen than the control group as a reaction to penalty. Using psychophysiological interaction analysis, we identified decreased functional connectivity between the right globus pallidus internus and the left anterior cingulate gyrus in the PD group. In contrast, increased connectivity between these structures was observed after penalty in the control group. Our results suggest altered functioning of the basal ganglia and their connections with the cortical structures involved in the limbic loop (e.g., the limbic fronto-striatal circuit of the basal ganglia) during decision-making in PD patients. Differences in the response to loss could be associated with insufficient negative reinforcement after a loss in PD patients in the ON state in comparison to a healthy population.

Keywords Parkinson's disease · Iowa Gambling Task · Decision-making · Dopamine · fMRI · Psychophysiological interactions

Introduction

The mesolimbic dopaminergic system is considered to be involved in motivation and sensitivity to reinforcement [1, 2], and it may influence decision-making through these processes. Many researchers have attempted to contribute to a better understanding of the influence of dopamine on decision-making by studying these processes in patients with Parkinson's disease (PD), for whom a malfunction of dopaminergic neurotransmission is characteristic [3–16].

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Indeed, there is emerging evidence for altered decision-making in patients with PD [3].

One of the most frequently employed instruments for testing decision-making is the Iowa Gambling Task (IGT) [17]. The task was designed to simulate real-life decision-making when the result is uncertain or ambiguous; namely, high immediate gains result in overall losses and are therefore disadvantageous from the view of long-term strategy [17]. Several studies that have used IGT with PD patients report impaired decision-making [5, 6, 9–11]. In a previous behavioral study, we revealed that early-onset PD patients were less competent as compared to control subjects in developing a strategy during IGT [16]. The present investigation was a continuation of this behavioral study. Using a different sample of PD patients, we sought to identify the functional anatomy of decision-making during IGT. We focused specifically on the final stage of the decision-making process—that is, on the evaluation of the result of an action [18].

Li and colleagues [19] reported the function of the following structures to be important for IGT performance: dorsolateral prefrontal cortex (DLPFC), suggested to be important for working memory; the insula and posterior cingulate cortex, implicated in the representation of emotional states; the mesial orbitofrontal cortex (OFC) and ventromedial prefrontal cortex, coupling the two previous processes; and the ventral striatum and anterior cingulate cortex (ACC)/supplementary motor area, implementing behavioral decisions. Other studies revealed the involvement of the amygdala (emotion system) [20] and hippocampus (memory system) [21] during IGT performance. Furthermore, Thiel and colleagues [15] reported decreased activation of right cingulate cortex, OFC, and frontomesial cortex—structures involved in the limbic loop of the basal ganglia—during IGT performance in PD patients relative to healthy controls.

Several hypotheses have been formulated in order to explain the impairments in decision-making observed in PD patients. One hypothesis focuses on the influence of dopaminergic therapy on cortico-striatal circuits. Interestingly, IGT performance in de novo PD patients without dopaminergic treatment is similar to that of age-matched healthy subjects (in contrast to patients on dopaminergic medication) [4]. Dopaminergic pathways have been implicated in cognitive functions such as value representation, weighing gains and losses, and choosing between alternatives [22]. Dopaminergic neurotransmission influences the ability to learn from negative and/or positive feedback; dopaminergic overstimulation enables the individual to learn more efficiently from the positive reinforcement of a gain and less efficiently from the negative reinforcement of a loss. Together with the above-mentioned findings, this suggests that decision-making impairment in PD patients is associated with dopaminergic overstimulation of the (orbital) fronto-striatal pathways after initiation of dopaminergic therapy [3]. Alternative hypotheses propose, for example, that impaired decision-making in PD patients is caused by cognitive impairment, or they associate poor IGT performance in PD patients with amygdala dysfunction [6]. Empirical studies, however, report results that contradict the cognitive impairment hypothesis [15, 23] and the amygdala dysfunction hypothesis [4, 12].

Based on the evidence presented above suggesting an influence of dopaminergic medication on reinforcement, the aim of the present study was to analyze the anatomical substrate of reinforcement for a gain or loss during the IGT in the PD patients in the ON state. Using the blood oxygen level-dependent (BOLD) signal as an index of neural activity, we used event-related functional magnetic resonance imaging (fMRI) to detect the brain structures engaged during the IGT. In light of the evidence cited above, revealing an influence of dopaminergic neurotransmission on the ability to learn from negative and/or positive reinforcement, we proposed the following hypotheses:

1. Any differences in IGT processing between PD patients and healthy subjects would be associated with an increased neural response to a win.
2. Any differences in IGT processing between PD patients and healthy subjects would be associated with a decreased neural response to a loss.
3. These two possibilities might not be mutually exclusive.

We employed a method for studying functional connectivity [psychophysical interactions (PPI)] in order to identify possible alterations of basal ganglia pathways. Neuronal pathways connecting the basal ganglia and the frontal cortex can be divided into loops (functionally segregated circuits); the involved cortical structures are OFC and ACC in the limbic loop and DLPFC in the cognitive loop [15]. Owing to the involvement of globus pallidus internus (GPi) in the limbic and cognitive loops [3, 15], we expected to observe differences between PD patients and control subjects in the degree of connectivity within both loops during the IGT, if a seed region was established in GPi. The importance of the right-sided network of cortical regions for performance of decision-making tasks in healthy subjects has been demonstrated [24]. Consistent with this, lower activation of prefrontal structures in the right hemisphere during the IGT has been reported in PD patients [15]. Furthermore, significantly poorer IGT performance in patients with right-sided rather than left-sided prefrontal lesions has been revealed [25]. Therefore, we selected the right GPi as our seed region.

Materials and methods

We examined 23 patients with Parkinson's disease on dopaminergic medication, recruited from the Brno Movement Disorders Centre database. Of the 23 patients selected, five were excluded from the study for one or more of the following reasons: (1) severe movement artifacts; (2) technical problems during scan acquisition; (3) invalid completion of IGT (i.e., more than 10 % of trials without the selection of a card within the time limit of 3.5 s). The resulting patient group included 18 patients (14 males, 4 females; mean age 52.67 ± 7.45 years). All the patients comprising this final sample met the United Kingdom Parkinson's Disease Brain Bank Criteria [26]. No genetic PD was detected. The average duration of PD was 6.33 ± 2.87 years. Patients were examined in the ON state—i.e., 2 h after the last medication intake with an absence of resting tremor or marked hypokinesia or rigidity. The average UPDRS III (Unified Parkinson's Disease Rating Scale, part III) score [27] was 18.89 ± 7.60. The average Hoehn and Yahr Scale [28] score was 1.97 ± 0.55. All the patients were on dopaminergic medication: two patients were on dopaminergic agonist in monotherapy; the majority used a combination of dopaminergic agonist and L-3,4-dihydroxyphenylalanine (L-DOPA); four patients also used a catechol-*O*-methyltransferase inhibitor. The average L-DOPA daily equivalent [29] was 1155.8 ± 862.5 (see Table 1).

Inclusion criteria were defined as: (1) an absence of cognitive impairment (MMSE cut off score was 27); (2) an absence of severe depression (Montgomery-Asberg Depression Rating Scale [30]); (3) no history of pathological gambling (according to the South Oaks Gambling Screen questionnaire [31] with the cut-off score of four, and the modified Minnesota Impulse Disorders Interview [32]).

The control group consisted of 22 age-matched subjects without any neurological condition. Four controls were excluded because of movement artifacts or incomplete task due to technical issues. Thus, the control group included 18 subjects (11 males, 7 females; mean age 50.61 ± 9.49 years). Written informed consent was obtained from all subjects and the study was approved by the Institutional Review Board of St. Anne's Hospital, Brno.

For a detailed description of IGT, see the Electronic Supplementary Material

Table 1 Demographic and clinical data

	PD group	Control group
Number of participants	18	18
Age (years)	52.67 (SD 7.45)	50.61 (SD 9.49)
Sex (male/female)	14/4	11/7
Average daily experience with computer (hours per day)	3.5 (SD 3.91)	2.3 (SD 1.81)
Education (university/A levels/other)	4/6/8	8/6/4
MMSE	29.7 (SD 0.69)	29.5 (SD 0.71)
Duration of PD (years)	6.33 (SD 2.87)	–
UPDRS III	18.89 (SD 7.60)	–
Hoehn and Yahr Scale score	1.97 (SD 0.55)	–
IGT score	−8.22 (SD 23.70)	8.67 (SD 26.24)

Functional MRI data acquisition

Data were acquired using a 1.5T Siemens Symphony scanner. A total of 524 functional scans were acquired during the IGT task using a gradient echo, echoplanar imaging sequence (TR = 2.3 s, TE = 40 ms, flip angle = 90°, field of view = 220 × 192.5 mm, matrix size = 64 × 56, in plane resolution = 3.44 × 3.44 mm, slice thickness = 5 mm, 26 transversal scans). Following the task, high-resolution anatomical T1-weighted images were acquired using a MPRAGE sequence (TR = 1.7 s, TE = 3.96 ms, flip angle = 15°, field of view = 246 × 246 mm, matrix size = 256 × 256, slice thickness = 1.17 mm, 160 sagittal slices).

All participants performed a 2-min training version of the IGT task prior to scanning. This version did not contain wins or losses. The aim was to familiarize participants with the testing program and the conditions inside the scanner.

Functional MRI data analysis

SPM5 toolbox (Functional Imaging Laboratory, the Wellcome Department of Imaging Neuroscience, Institute of Neurology at University College London, UK, 2005) running under MATLAB 7.10 (Mathworks Inc., USA) was employed for data processing and analyses. Each subject's time series was preprocessed using the same order of steps: (1) realignment to the first scan, (2) co-registration with anatomical image, (3) spatial normalization to fit the standard anatomical space (MNI, parameters derived using anatomical image), (4) resampling to a resolution of 3 × 3 × 3 mm, and (5) spatial smoothing using a Gaussian filter (FWHM = 8 mm). Subsequently, periods longer than 128 s were removed from the time series of each voxel to filter out physiological noise.

The goal of the following statistical analysis was to examine whether between-group differences existed in

the BOLD signal measured at the moment when the subject becomes aware of a win or loss on each trial. Trials were categorized as positive, negative, or zero outcome. In each trial, we were interested in the reaction of subjects to feedback, during which the trial balance was revealed. An individualized general linear model (GLM) was applied for each subject. The design matrix included three regressors that modeled the response to each of the three types of trials (trial timing function convolved with canonical hemodynamic response function). Movement parameters (estimated during functional scan realignment) were included as nuisance regressors to model possible residual motion effects. An autoregressive model was employed during GLM estimation to account for serial autocorrelation in the data. Statistical parametric maps with t statistics were computed to assess the effects of positive- and negative-outcome regressors. Corresponding contrast files were carried into the second-level analysis (two-sample t tests) to assess group differences (e.g., contrast between both groups, separately for a case of positive, negative, or zero outcome). The cluster-level inference method was used to set the significance level. An initial cut-off was set at a t value equivalent to $p < 0.001$, uncorrected, and clusters with $p < 0.05$ corrected for FWE using random field theory [35] were determined to be significant [36].

Psychophysiological interaction (PPI) analysis was applied in order to determine alterations in functional integration within the basal ganglia circuits. This method detects changes in functional connectivity between a seed region and the rest of the brain in reaction to a defined event within the experimental context [37].

The right globus pallidus internus (GPi; $x = 12$, $y = -1$, $z = -3$) was chosen as the seed location (see above). For all subjects, the BOLD signal was extracted from a sphere centered at the seed location (6 mm radius) as a first eigenvariate. This signal was adjusted by removing the estimates of physiologic noise (movement parameters, signal from white matter and ventricles). Interactions between this signal and the three types of trial (positive, negative, and zero outcome) were computed in SPM5. Again, the GLM was set individually for each subject. The design matrix included the seed signal, the three regressors modeling the response to the three trial types, three interaction regressors, and nuisance regressors that modeled the physiological noise. Parametric t statistic maps were computed for the interaction regressors (for positive and negative outcome), and corresponding contrast files were carried into the second-level random effects analysis, comprising both one- (single group means) and two-sample t tests (between-group comparisons). The significance level was set as described above.

Results

Behavioral data

In terms of IGT performance, PD patients achieved a lower total IGT score than healthy controls (patients: -8.22 ± 23.70; controls: $+8.67 \pm 26.24$), but this difference was not statistically significant ($p > 0.100$) (Fig. 1). The analysis of partial IGT scores revealed differences between the groups in performance improvements over time; namely, patients achieved lower IGT scores compared to controls in the second (-1.00 vs. 0.56), third (-1.33 vs. 3.78) and fourth (-3.03 vs. 3.44) blocks (see Fig. 2). After multiple-comparison correction (Bonferroni), however, this difference only approached statistical significance on block four ($H_{(1)} = 5.648$; $p_{\text{corr}} = 0.051$).

We observed no differences between patients and controls in the reaction to win trials as assessed by shift patterns. A difference between the groups was revealed in the response to loss trials, however. Specifically, patients were more likely to persevere with disadvantageous deck B following a loss from that same deck ($H_{(1)} = 5.98$; $p_{\text{corr}} = 0.042$; $d = -0.41$).

No significant correlations were found between total IGT score and L-DOPA daily equivalent, UPDRS III score,

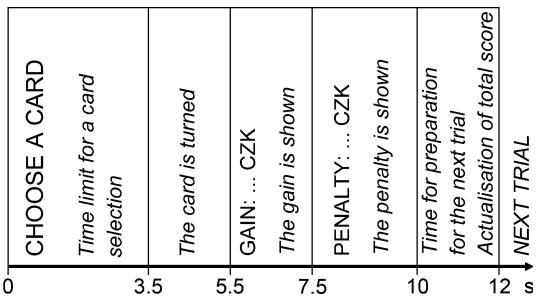

Fig. 1 Time schedule of computerized version of the IGT (adapted from Fukui et al. [33], modified)

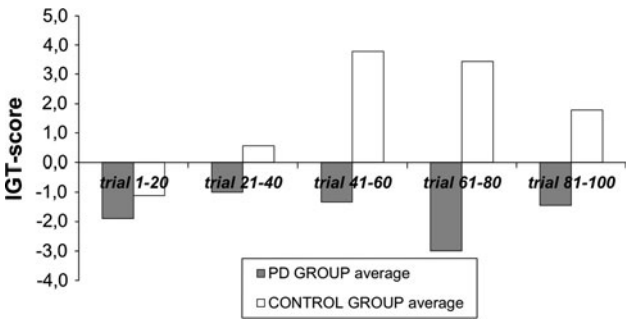

Fig. 2 IGT scores during Iowa Gambling Task performance

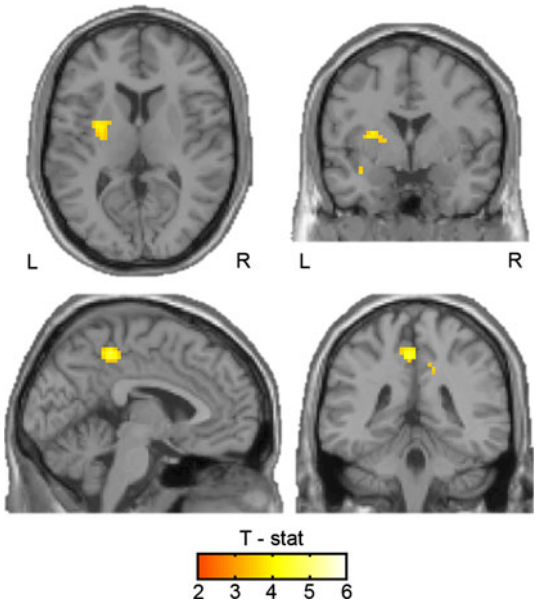

Fig. 3 Activation after penalty and after gain—control group vs. PD group. Activation after penalty (*above*), control group vs. PD group: left putamen, $p < 0.050$ corrected, cluster-level inference. Activation after gain (*below*), control group vs. PD group: left posterior cingulum, $p = 0.059$ corrected, cluster-level inference

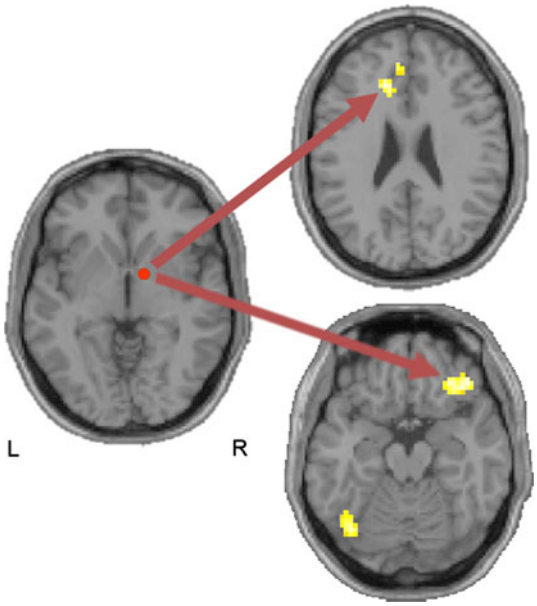

Fig. 4 Psychophysiological interactions—changes in functional connectivity as a reaction to penalty in PD group. Seed: right globus pallidus internus $x = 12$, $y = -1$, $z = -3$. Left anterior cingulate gyrus (*above*), $p = 0.085$ corrected, cluster-level inference after receiving a penalty, functional connectivity decreases. Right orbitofrontal cortex (*below*), $p = 0.085$ corrected, cluster-level inference after receiving a penalty, functional connectivity decreases

Hoehn and Yahr scale score, or disease duration in the PD patients.

fMRI data

We identified significantly lower activation of the left putamen following a loss (i.e., at the moment a penalty is displayed on the screen) in the PD group when compared with the control group ($p < 0.050$ corrected, cluster-level inference; see Fig. 3). When analyzing responses to wins, however, no significant cluster emerged. A slightly lower activation of the left posterior cingulate cortex was observed in the PD group relative to the control group ($p = 0.059$; see Fig. 3).

Using PPI, we identified changes in functional connectivity with the right GPi following the experience of a loss; specifically, in the PD group, we observed a slightly decreased connectivity between GPi and right OFC ($p = 0.085$; see Fig. 4), and between GPi and left ACC ($p = 0.085$; see Fig. 4). The between-group comparison revealed a significant difference in left ACC ($p < 0.050$ corrected, cluster-level inference; see Fig. 5). Moreover, in reaction to a loss, the connectivity between the left ACC and right GPi decreased in the PD group, but increased in the control group.

The PPI analysis on winning trials identified no significant cluster in which functional connectivity expressed a between-group difference, nor a change of connectivity in PD patients following the experience of a win.

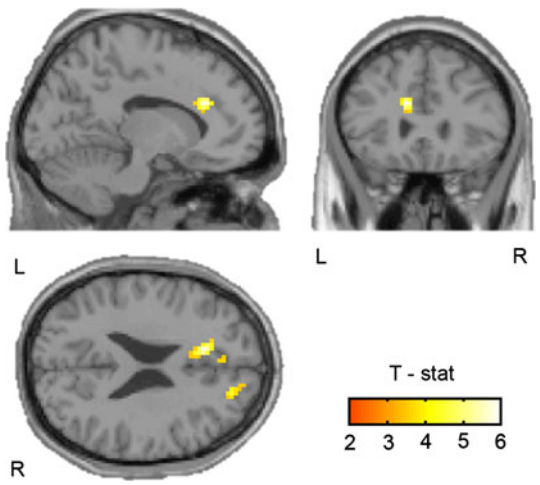

Fig. 5 Psychophysiological interactions—changes in functional connectivity as a reaction to penalty; control group vs. PD group. Left anterior cingulate gyrus, $p < 0.050$ corrected, cluster-level inference after receiving a penalty, functional connectivity between the seed and this area increases in control group and decreases in PD group

Discussion

The aim of this study was to investigate the functional anatomy of decision-making in a sample of PD patients compared to healthy controls. Specifically, we investigated whether or not these groups differed in their reaction to

wins or losses during IGT. Behaviorally, we revealed subtle, but meaningful differences between the two groups in IGT performance. Not only did patients appear less able to acquire an effective strategy over time, they also demonstrated a tendency to persevere with deck B following a loss. Given that a selection from deck B carries the greatest risk of losing everything that has been gained, this is indicative of an impaired response to a loss.

Measuring the BOLD signal, we observed the lower engagement of a region of the basal ganglia (left putamen) in reaction to a loss in a sample of patients relative to controls. The basal ganglia are assumed to be involved in reward expectation and they are considered important for value representation [22]. Reduced activation of the basal ganglia in PD patients (for whom basal ganglia dysfunction is characteristic) was an expected result. We would like to stress that this reduced response was observed only in the case of a loss—the activation of basal ganglia structures was equivalent in both groups during win trials. These results suggest insufficient processing (or altered reinforcement) of a penalty in PD patients.

We consider decreased functional connectivity between the right GPi and ACC in reaction to a loss a very interesting finding, because it indicates altered integration of structures involved in the limbic loop of the basal ganglia. This would be consistent with the putative impairment of the orbitofronto-striatal circuits [3]. ACC is involved in conflict detection and in error-related processing—for example, when a discrepancy occurs between an expected outcome and the actual outcome and such processing might assist healthy subjects in leaving an unsuccessful strategy. By integrating successes and errors over time, ACC is also associated with processes of uncertainty [18, 19]. Furthermore, ACC is among the structures considered to be involved in punishment processing [38]. As such, decreased connectivity between GPi and ACC as a reaction to a penalty may be a correlate of impaired punishment processing in PD patients.

We found no differences in the response of DLPFC, a cortical structure involved in the cognitive loop as reported in the positron emission tomography (PET) study by Thiel and colleagues [15]. We also found no indications of amygdala dysfunction. Instead, our results indicate an influence of fronto-striatal circuits dysfunction—mainly the limbic loop—on the decision-making impairments observed in PD patients.

Although some non-significant changes in functional connectivity were observed between PD patients in the ON state and control subjects after reward notification, the major differences in BOLD signal were found at the moment of penalty appearance. We suggest that this observation results from impaired negative reinforcement of penalty, which would leave decision-making in the PD patients influenced more by gains than losses. This would be in agreement with the reported findings on the influence of dopamine during learning and decision-making [3].

The differences observed between PD patients and controls in the processing of loss could (at least partly) result from the game design itself. Each card from the same deck leads to the same amount of win—therefore, the plus sum is expected. Loss, on the other hand, comes as a surprise for the player. Therefore, the importance of the penalty could be increased artificially by its aspect of novelty. Future studies might consider using a modified version of IGT with expected penalties and unexpected gains in a sample of PD patients.

Another issue is the potential influence of medication type on IGT performance. A clear association between medication type and/or dose has not been demonstrated at the behavioral level [5], and we observed no associations between total IGT score and L-DOPA daily equivalent. It is possible that such an association could be found on the neurophysiological level (using fMRI), however. Our small sample PD patients formed a relatively homogenous group with regard to the medication. Additional research with more extensive and/or more heterogeneous PD samples might advance our understanding on the matter.

Interestingly, we observed no associations between total IGT score, disease duration, UPDRS III score, or Hoehn and Yahr scale, consistent with previous findings [3]. It has been suggested that impaired decision-making does not progress simultaneously with impaired motor function or that potential compensatory mechanisms moderate the further deterioration of decision-making [5].

We must also mention behavioral data: when we compared IGT performance between our PD group and our control group, we found no significant difference in total IGT scores; using more detailed analysis, we observed subtle differences that indicate a less effective strategy in PD patients. An analogous situation occurred in our recent behavioral study using early-onset PD patients [16].

The results of studies employing IGT with PD patients are inconsistent; while some reveal impairments in decision-making in patient populations [5, 6, 9–11], others report equivalent performance in decision-making tasks between PD patients and healthy controls [7, 8, 12–14]. A possible explanation for inconsistencies in this area could be that a total IGT score—the most frequently used indicator of success in IGT—has certain limitations. Buelow, for example, argues that the use of a composite IGT score is a major factor leading to inconsistencies in the IGT literature [34].

It is important to mention the potential limitations of the present study. We acknowledge that by focusing our neurophysiological analyses on the reaction to win or loss addresses only one aspect of IGT performance. A full

description of performance is far more complex, as our behavioral data suggest. Using IGT in an event-related fMRI study is limited by the relatively low amount of target events. Moreover, MRI contraindications exclude certain groups of subjects—for instance, individuals with deep brain stimulation or severe dyskinesias could not be examined. This necessarily restricts the selection of patients with this diagnosis, and limits the generalization of findings from fMRI studies to specific PD populations. Secondly, only a crude assessment of cognitive impairment was performed. Importantly, however, the majority of IGT studies report no significant relationship between cognitive functions and IGT performance in various samples [23], including PD patients [3, 16]. This was the case in our earlier study with early-onset PD patients, where the IGT performance was unrelated to executive function. Moreover, poorer performance in IGT might reflect different cognitive processes than those evaluated by standard neuropsychological tests (e.g., Stroop test, Tower of London). It was for these reasons that detailed assessment of cognitive function was not conducted. Nevertheless, by incorporating more detailed assessment of cognitive functions, future studies might unveil the mechanisms underlying abnormal decision-making.

Conclusion

Using event-related fMRI, we revealed significant differences in the neural response to penalty between PD patients on dopaminergic medication in the ON state and control subjects; differences observed in reaction to a reward were inconsistent and did not reach statistical significance. These results might suggest that PD patients evaluate penalty inadequately, which may lead to insufficient negative reinforcement of loss. We observed reduced activation of the left putamen after a penalty in PD patients when compared with control subjects. Furthermore, we observed decreased functional connectivity between the basal ganglia (right GPi) and left ACC in response to a penalty in PD patients when compared with controls. In contrast, connectivity in the same situation increased in our sample of healthy controls. Our results indicate an altered function of the basal ganglia and their connections with the cortical structures involved in the limbic loop during decision-making in PD patients in the ON state.

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Ethical standards The study has been approved by appropriate ethics committee and has therefore been performed in accordance with ethical standards laid down in the 1964 declaration of Helsinki.

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